The dual role of the crosstalk between autophagy and ferroptosis in lung cancer treatment: Advances in mechanisms and therapeutic strategies (Review)

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Abstract. The interaction between autophagy and ferroptosis has resulted in the identification of novel approaches for the treatment of lung cancer (LC). The two processes are closely interconnected via three core regulatory modes: Negative regulation, positive regulation and feedback regulation, thereby forming a complex and context-dependent regulatory network. Within the context of LC progression, the interaction between autophagy and ferroptosis exhibits a dual role. On one hand, it promotes LC development by enabling cancer cell survival in adverse microenvironments, remodeling metabolic pathways and orchestrating the tumor microenvironment to facilitate immune evasion. On the other hand, it can suppress LC by removing damaged cellular components, inducing ferroptosis, and boosting immune surveillance and clearance of cancer cells. Consequently, therapeutic strategies for LC are continuously evolving. In the field of pharmacotherapy, traditional agents such as chloroquine and its derivatives are being repurposed with subtype-dependent efficacy, and their antitumor activity can be potentiated via nanoparticle delivery systems. When combined with ferroptosis inducers or other drugs, these agents can augment therapeutic efficacy and surmount drug resistance. Current research and development efforts are focused on small-molecule compounds that target key nodes in autophagy-ferroptosis crosstalk. Moreover, combination therapy represents a central focus of research. When combined with chemotherapy, radiotherapy, targeted therapy and immunotherapy, this combination approach shows potential for synergistic efficacy. However, current research faces several challenges, including the complexity of regulatory mechanisms and inter-individual variability. Most therapeutic strategies remain in the preclinical research phase and the synergistic mechanisms of combination therapies are not yet fully elucidated. Comprehensive investigations into the molecular processes, coupled with the application of multi-omics technologies, are crucial for clarifying the regulatory network. The development of precise biomarkers, along with the integration of artificial intelligence and big data analytics, is essential to accelerate the advancement of novel drugs and therapeutic strategies, with the ultimate goal of improving the prognosis for patients with LC.

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1. Introduction

Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide (1). Although standard therapeutic modalities, including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, have improved, their clinical efficacy is often compromised by drug resistance, tumor microenvironment remodeling and immune evasion (2). Recent breakthroughs in understanding programmed cell death (PCD) pathways have resulted in the identification of novel therapeutic options. In particular, the close crosstalk between autophagy and ferroptosis has emerged as a critical regulatory axis with notable implications for LC treatment (3).

Autophagy is an evolutionarily conserved homeostatic process that exerts a context-dependent role in tumorigenesis. While it can promote tumor cell survival under metabolic stress by recycling cellular components (4), it may also

trigger tumor-suppressive effects through autophagic cell death (5). Moreover, autophagy actively shapes the tumor immune microenvironment. For example, the microRNA (miR)-127-3p/MAPK/AKT/mechanistic target of rapamycin (mTOR)/p70S6K axis has been shown to simultaneously stimulate tumor cell autophagy and polarize macrophages toward an M1 phenotype (6).

Ferroptosis, by contrast, is a distinct form of PCD driven by iron-dependent lipid peroxidation, leading to membrane damage and cell death (7). It is tightly regulated by molecules including glutathione peroxidase 4 (GPX4), iron metabolism proteins such as ferritin heavy chain 1 (FTH1), and the cystine/glutamate antiporter system Xc^- (7,8). Preclinical studies have consistently demonstrated that triggering ferroptosis effectively suppresses LC growth, underscoring its therapeutic potential (9,10). Lung adenocarcinoma (LUAD) exhibits particular susceptibility to ferroptosis modulation and acquired resistance to this process represents a recognized barrier to treatment efficacy (11,12).

The interaction between autophagy and ferroptosis is complex and biologically consequential. Autophagic degradation of substrates such as ferritin and GPX4 can elevate intracellular iron and lipid peroxides, thereby eliciting ferroptosis and stimulating antitumor immunity in non-small cell LC (NSCLC) (13). This crosstalk is especially pertinent in LC given the characteristic dysregulation of iron metabolism, oxidative stress responses and autophagic flux in this disease. Notably, O-GlcNAcylation has been shown to co-regulate ferritinophagy and mitophagy to fine-tune ferroptosis sensitivity in LC cells (14).

Despite growing research interest, critical knowledge gaps persist. First, existing reviews lack a systematic synthesis of LC-specific crosstalk patterns and subtype heterogeneity. Second, the roles of emerging post-translational modifications in mediating this interaction are not fully integrated into current models. Third, the contribution of this axis to therapy resistance and its potential as a therapeutic target requires a more comprehensive analysis. Finally, the translational relevance, including novel biomarkers and therapeutic agents, has not been adequately addressed.

Therefore, an improved mechanistic understanding of the autophagy-ferroptosis interplay is essential for elucidating the pathogenesis of LC and developing innovative treatment strategies. The present review aims to address these gaps by providing an updated, LC-focused summary of this crosstalk, spanning molecular mechanisms to therapeutic translation, thereby offering a solid foundation for future research and clinical development.

2. Fundamental insights into autophagy and ferroptosis

Molecular mechanisms and biological functions of autophagy. Autophagy is a highly organized catabolic process essential for cellular homeostasis. Its initiation is triggered by stressors such as nutrient deprivation or oxidative stress, which activate the unc-51 like kinase 1 (ULK1) complex. ULK1 directly interacts with lactate dehydrogenase (LDH)A, phosphorylates serine-196 and elevates intracellular lactate levels. This promotes lactylation of vacuolar protein sorting 34 (VPS34), which in turn amplifies autophagic flux and endolysosomal trafficking (15). VPS34, a class III PI3K, produces phosphatidylinositol-3-phosphate to recruit autophagy-related (ATG) proteins and initiate autophagosome nucleation (16). This cascade is not merely a housekeeping pathway but a dynamic stress response. For example, in $KRAS^{G12C}$-driven LC cells, $KRAS^{G12C}$ inhibition induces ULK1/2-mediated autophagy as a critical survival mechanism, highlighting its potential as a pharmacological target (17). However, this dependency is likely not universal and a systematic understanding of how different oncogenic drivers rewire autophagic networks remains to be elucidated.

Autophagosome elongation and maturation rely on two ubiquitin-like conjugation systems. The ATG12-ATG5-ATG16L1 complex drives membrane expansion (18), whereas microtubule-associated protein 1 light chain 3 (LC3) is conjugated to phosphatidylethanolamine, converting LC3-I to membrane-bound LC3-II, a hallmark of autophagosomes (19). Mature autophagosomes fuse with lysosomes to form autolysosomes, where engulfed cargo is degraded and recycled.

Autophagy serves pivotal roles in postembryonic development, cell differentiation and modulation of the inflammatory response, and its dysregulation is implicated in various diseases (20,21). In LC, autophagy exerts context-dependent effects. For example, ailanthone blocks autophagy by upregulating growth arrest specific (GAS)5 via inhibition of up-frameshift protein 1-mediated nonsense-mediated mRNA decay, thereby inhibiting NSCLC proliferation (22). Conversely, regulator of G protein signaling 20 facilitates NSCLC proliferation by activating autophagy through suppressing the PKA-Hippo pathway (23). Furthermore, the long non-coding (lnc)RNA KCTD21-AS1, modified by METTL14-mediated N6-methyladenosine methylation, acts as a competing endogenous RNA for miR-519d-5p to regulate CD47 and TIPRL expression, thereby modulating macrophage phagocytosis and autophagy in LC cells (24). In small cell LC (SCLC), elevated AMBRA1 promotes CDK6 degradation via autophagy and confers a favorable prognosis in patients (25). These studies collectively argue against targeting autophagy as a monotherapy; instead, they argue for a precision medicine approach based on tumor genotype and autophagic cargo specificity.

Definition, characteristics and mechanisms of ferroptosis. Ferroptosis is a distinct form of PCD driven by iron-dependent lipid peroxidation. Its core mechanisms involve dysregulated iron metabolism, excessive lipid peroxidation and compromised antioxidant defense (26).

Cellular iron uptake is primarily mediated by the transferrin receptor. Intracellularly, iron is stored in ferritin to maintain homeostasis; dysregulation increases the labile iron pool, which catalyzes the Fenton reaction to generate hydroxyl radicals that initiate lipid peroxidation (27). This process is central to ferroptosis: Polyunsaturated fatty acids within cellular membranes are peroxidized to form lipid hydroperoxides (LOOH). Under normal conditions, the glutathione (GSH)-GPX4 axis reduces LOOH to nontoxic alcohols, preserving membrane integrity (28). Depletion of GSH or inactivation of GPX4 leads to LOOH accumulation, resulting in the buildup of toxic peroxidation products, consequent membrane damage, and cell

death (29). Other antioxidant systems, including superoxide dismutase and catalase, provide additional protection against oxidative stress. However, the clinical translatability of these *in vitro* findings remain equivocal owing to the absence of corroborative human tissue or cohort data.

In NSCLC, ferroptosis is regulated by diverse molecular pathways. For example, exosomal ROR1-AS1 from cancer-associated fibroblasts suppresses ferroptosis by stabilizing solute carrier family 7 member 11 (SLC7A11) mRNA via insulin-like growth factor 2 mRNA binding protein 1, thereby enhancing cystine uptake and GSH synthesis (30). Similarly, lysosome associated protein transmembrane 4B (LAPTM4B) blocks ferroptosis by suppressing NEDD4L/ZRANB1-mediated ubiquitination and degradation of SLC7A11 (31). Conversely, other mechanisms promote ferroptosis. Combined suppression of STAT3 and HOXC10 induces ferroptosis, effectively suppressing bone metastasis in KRAS-mutant LC (32). Oncogenic RIT1 mutations not only activate canonical RAS/MAPK and PI3K/AKT pathways but also modulate nuclear factor, erythroid 2 like 2 (NRF2) target expression, markedly increasing cellular susceptibility to ferroptosis inducers (33). Notably, a number of ferroptosis-regulating pathways intersect with autophagy networks, forming a complex interactive landscape.

Critical perspectives and unresolved questions. While the core frameworks of autophagy and ferroptosis are established, their functional heterogeneity in LC presents notable dichotomies. The determinants of this duality, such as upstream signaling pathways or driver mutations, remain unclear. In ferroptosis, GPX4, typically a suppressor, paradoxically sensitizes GPX4-overexpressing NSCLC cells to RAS selective lethal 3 (RSL3)-induced ferroptosis (34). Similarly, SLC7A11 can be upregulated by LAPTM4B to inhibit ferroptosis or downregulated by circPOLA2 to promote it (35), yet the contextual switches governing its function are unknown.

These contradictions highlight critical questions: How do LC-specific adaptations of autophagy and ferroptosis differ from those in normal lung epithelium? Can these differences be therapeutically exploited? Future research should employ subtype-specific models and single-cell multi-omics to map molecular signatures, clarify how driver mutations shape pathway heterogeneity and validate these insights for targeted therapy development.

3. Regulatory mechanisms of autophagy and ferroptosis crosstalk

Negative regulation. Autophagy can act as a context-dependent negative regulator of ferroptosis, a pathway frequently dysregulated in LC that fosters tumor cell survival and therapy resistance. By degrading lipid peroxidation-derived peroxisomes, misfolded proteins and damaged organelles, autophagy helps maintain redox homeostasis and suppresses ferroptosis (36,37).

This regulatory interplay involves crosstalk with other cell death pathways. Autophagy can modulate the expression and activity of apoptosis-related proteins, thereby indirectly altering cellular susceptibility to ferroptosis (38). Furthermore, mechanical tension has been shown to govern iron metabolism via nuclear receptor coactivator 4 (NCOA4)-FTH1 phase-separation-mediated autophagy, influencing ferroptosis sensitivity (39).

mTOR serves as a central nutrient and energy sensor within this network (40). Under nutrient-replete conditions, activated mTOR suppresses autophagy and strengthens antioxidant defenses, thereby restraining ferroptosis. Conversely, stress conditions inhibit mTOR, triggering autophagy and metabolic reprogramming that sensitize cells to ferroptosis. In LC, Plin2 drives NSCLC proliferation by inhibiting autophagy via AKT/mTOR activation (41), whereas circFAM190B propels tumor progression by suppressing autophagy through the SFN/mTOR/ULK1 axis (42). The compound (+)-anthrabenzoxocinone inhibits PI3K/AKT/mTOR signaling, inducing cell cycle arrest, apoptosis and autophagy, while elevating reactive oxygen species (ROS) in NSCLC cells (43). However, the specific downstream effectors of PI3K/AKT/mTOR that mediate autophagy-ferroptosis crosstalk, along with potential subtype-specific differences, require further definition.

Mitophagy, the selective autophagic clearance of mitochondria, serves a key inhibitory role against ferroptosis (44). During mitophagy, mitochondria undergo characteristic morphological changes, including swelling, cristae rupture and vacuolization, which are distinct from the cristae reduction and fragmentation observed in ferroptosis (45). Tumor cells deficient in mitophagy exhibit heightened susceptibility to ferroptosis inducers due to the loss of this protective mechanism (46). Molecules such as fibroblast growth factor 21 (47), BCL2 interacting protein 3/NIP3-like protein X (48) and acteoside (via the NRF2-mitophagy axis) (49) mitigate ferroptosis by restoring mitochondrial function or removing damaged mitochondria, underscoring the protective role of mitophagy against ferroptosis.

Positive regulation. Under specific conditions, autophagy can promote ferroptosis, a switch often associated with malignant progression in LC. Overactivation of ferritinophagy drives rapid ferritin degradation, releasing free iron that catalyzes lipid peroxidation and induces ferroptosis (50,51). Additional promoting mechanisms include Par-4-stimulated, NCOA4-mediated ferritinophagy (52) and autophagic degradation of GSH reductase, which reduces GSH synthesis and antioxidant capacity, further promoting ferroptosis (53).

In LC, depletion of ubiquitin-specific peptidase (USP)13 facilitates the transition from autophagy to ferroptosis in KRAS-mutant LUAD cells via the NRF2-p62-kelch like ECH associated protein 1 (KEAP1) axis (54). Rapamycin, a classical autophagy inducer, can exacerbate mitochondrial damage and provoke ferroptosis when combined with multi-walled carbon nanotubes (55). Beclin-1 also induces autophagy-triggered ferroptosis by upregulating ATG5 (56).

Cytochrome *c* oxidase subunit 7A1 (COX7A1) exhibits a distinct dual role: It enhances mitochondrial metabolism to sensitize NSCLC cells to cysteine deprivation-induced ferroptosis, while concurrently inhibiting autophagy to block mitochondrial remodeling, two seemingly opposing effects. Rapamycin can reverse COX7A1-mediated autophagy blockade, synergistically enhancing ferroptosis under cysteine deprivation (57). The molecular switch controlling the opposing functions of COX7A1remains unknown, limiting its

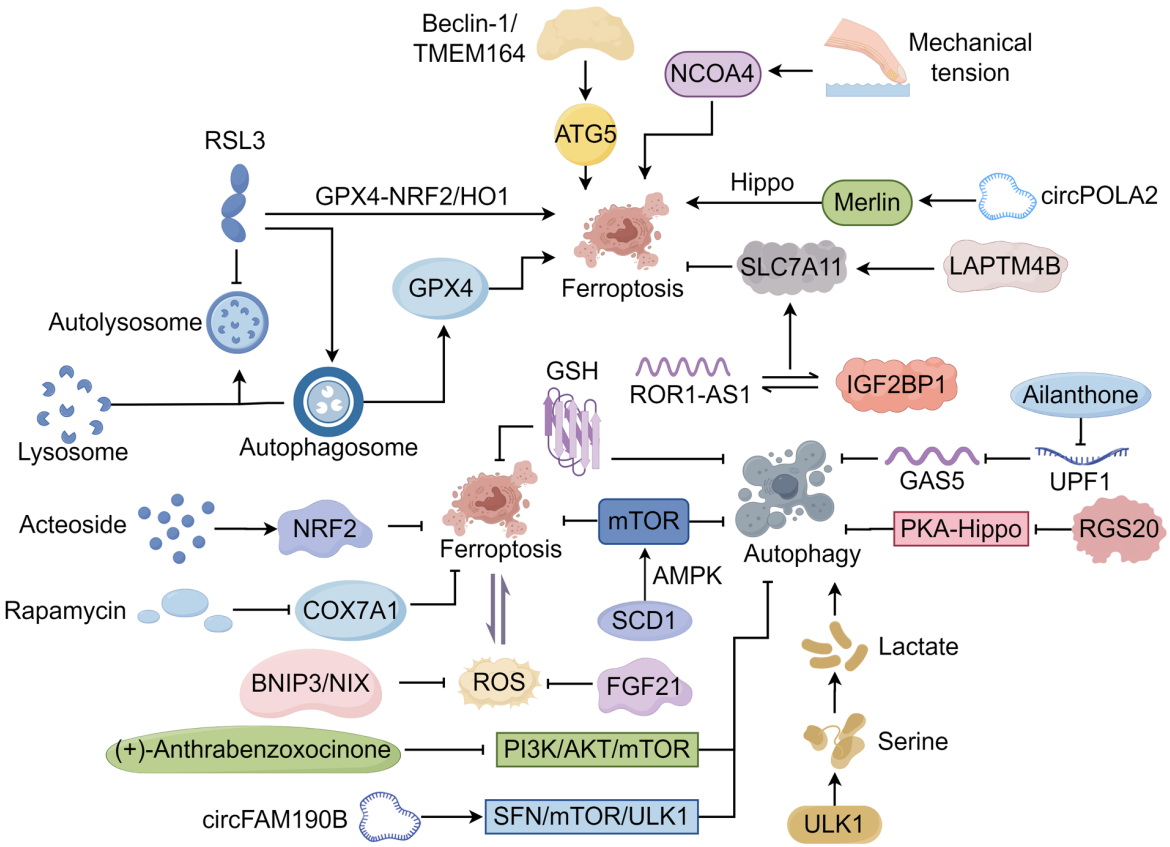

Figure 1. Mechanisms of autophagy and ferroptosis, and the regulatory mechanisms between them. The figure was created by Figdraw (www.figdraw.com). RSL3, RAS selective lethal 3; GPX4, glutathione peroxidase 4; TMEM164, transmembrane protein 164; ATG5, autophagy related 5; NCOA4, nuclear receptor coactivator 4; LAPTM4B, lysosome associated protein transmembrane 4B; SLC7A11, solute carrier family 7 member 11; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; GSH, glutathione; UPF1, up-frameshift protein 1; GAS5, growth arrest specific 5; RGS20, regulator of G protein signaling 20; SCD1, stearoyl-CoA desaturase 1; FGF21, fibroblast growth factor 21; ROS, reactive oxygen species; BNIP3, BCL2 interacting protein 3; NIX, NIP3-like protein X; COX7A1, cytochrome *c* oxidase subunit 7A1; NRF2, nuclear factor, erythroid 2 like 2; ULK1, Unc-51 like kinase 1; mTOR, mechanistic target of rapamycin.

therapeutic exploitation. The core mechanisms of autophagy, ferroptosis and their crosstalk are summarized in Fig. 1.

Feedback regulation of autophagy by ferroptosis. Ferroptosis, through its associated oxidative stress and iron dysregulation, can reciprocally modulate autophagy, forming a dynamic bidirectional network crucial for cell fate decisions in the tumor microenvironment.

Under ferroptotic stress, JNK activation leads to phosphorylation of Beclin-1 at Ser90/93, strengthening its interaction with the VPS34 complex and stimulating autophagosome formation (58,59). This constitutes an adaptive response to ferroptosis-induced damage.

Iron overload enhances p62 phosphorylation, which strengthens its binding to KEAP1 and leads to NRF2 release and nuclear translocation. NRF2 then transcriptionally activates ATG genes, helping to mitigate ROS and maintain homeostasis (60-62). A critical unresolved question is how NRF2 balances autophagy activation and ferroptosis mitigation in the LC microenvironment, as this balance may determine tumor cell fate and therapeutic response.

Ferroptosis-associated oxidative stress also influences post-translational modifications of ATG proteins, fine-tuning their activity and localization (63-65). Ubiquitin ligase subunit FBXO9 blocks V-ATPase assembly to impede LC metastasis (66). Additionally, ferroptosis-derived ROS can activate the AMPK/ULK1 pathway to initiate autophagy (67), although the precise molecular cascade in LC cells is not fully elucidated. In summary, the crosstalk between autophagy and ferroptosis is governed by a complex, context-dependent network encompassing three core modes: i) Negative regulation, primarily through mTOR signaling and mitophagy, to inhibit ferroptosis; ii) positive regulation, driven by ferritinophagy overactivation, degradation of antioxidant proteins and regulators such as USP13, to promote ferroptosis; iii) feedback regulation, involving the JNK/Beclin-1, NRF2/p62 and ROS/AMPK pathways, creating a bidirectional adaptive loop. A defining feature is the dual role of autophagy, which can either suppress or induce ferroptosis depending on the genetic background, LC subtype and microenvironmental cues. Critical unresolved issues include identifying the molecular switches that govern the transition of autophagy from an anti- to a pro-ferroptotic state, elucidating subtype-specific differences in crosstalk mechanisms, and clarifying the molecular basis underlying proteins such as COX7A1 to exhibit opposing functions. Addressing these questions is essential for deciphering LC cell survival strategies and developing targeted therapies that exploit this dynamic interplay.

4. Dual role of autophagy-ferroptosis crosstalk in LC

The interplay between autophagy and ferroptosis exerts a marked yet context-dependent influence on LC progression,

functioning as a precise biological rheostat that can be co-opted to either promote tumor progression or trigger tumor suppression.

Tumor-promoting effects. The nutrient-deprived and hypoxic tumor microenvironment of LC frequently drives the exploitation of autophagy as a cytoprotective mechanism that counteracts ferroptosis. This mechanism maintains redox homeostasis, enabling cancer cell proliferation under hostile microenvironmental stress. Genetic or pharmacological inhibition of core autophagy machinery undoes this protective mechanism, markedly sensitizing LC cells to ferroptosis inducers. For example, in cells expressing an active Rab37 mutant, knockdown of ATG5/7 not only reduces autophagic flux but also diminishes tissue inhibitor of metalloproteinase 1 secretion, leading to suppressed lung nodule formation and metastasis (68). This evidence underscores the effects of autophagy as a critical adaptive response, and demonstrates that its disruption unveils a latent vulnerability to ferroptotic death.

The regulatory interplay between autophagy and ferroptosis notably influences both the survival and metabolic processes of LC cells, particularly through metabolic remodeling. A key adaptation is the enhancement of fatty acid oxidation; a process associated with aggressive proliferation and poor patient prognosis (69,70). Dysregulated fatty acid metabolism fuels proliferation and confers targeted-therapy resistance in liver tumors; whether an analogous axis operates in LC, and whether it is further modulated by autophagy and ferroptosis, remains to be investigated (71). Furthermore, lipid metabolism enzymes directly interface with this axis. For example, stearoyl-CoA desaturase 1 suppresses autophagy by tuning lipid peroxidation and the mTOR pathway, thereby promoting NSCLC proliferation and metastasis (72). This suggests that metabolic rewiring via lipid pathways is a non-canonical mechanism by which the autophagy-ferroptosis balance is tilted toward tumor promotion.

Beyond cell-intrinsic effects, this crosstalk actively sculpts an immunosuppressive microenvironment. Autophagy can induce the secretion of immunosuppressive cytokines and regulate the expression of immune checkpoints such as PD-L1 (73). It also facilitates crosstalk with tumor-associated macrophages, particularly the M2 phenotype, to further dampen antitumor immunity. Consequently, strategic inhibition of autophagy has been shown to restore antigen presentation and synergize with immunotherapy in preclinical NSCLC models (74). These findings suggest that high baseline autophagic activity, particularly when coupled with elevated checkpoint expression, could serve as a biomarker for identifying patients who may benefit from combining autophagy inhibitors with immunotherapy, a hypothesis awaiting robust clinical validation.

Tumor-suppressive effects

Inducing ferroptotic cell death. Paradoxically, under specific pharmacological or genetic perturbations, autophagy can function as a tumor suppressor by actively promoting ferroptosis. Agents such as rapamycin or curcumin enhance autophagic flux, leading to the degradation of key anti-ferroptotic proteins such as GPX4; this depletes cellular antioxidant defenses, resulting in uncontrolled lipid peroxidation and execution of ferroptosis (57,75). Similarly, non-pharmacological interventions such as plasma-activated medium therapy can induce LC cell death via ferroptosis pathways (76). However, the complexity is highlighted by paradoxical regulators; for example, the autophagy receptor hippocalcin-like 1 (HPCAL1) promotes ferroptosis yet paradoxically facilitates NSCLC growth *in vivo*, suggesting that its net oncogenic role may involve pleiotropic functions beyond regulating this cell death pathway (77).

Enhancing antitumor immunity. The tumor-suppressive function extends to potentiation of antitumor immunity. Autophagy amplifies antigen processing and presentation, enhancing T-cell activation and antitumor immunity (78,79). Furthermore, ferroptosis itself is an immunogenic form of cell death; its induction can release damage-associated molecular patterns and tumor antigens, thereby remodeling the tumor immune landscape (80). This synergy is exemplified by transmembrane protein 164 (TMEM164), which promotes autophagy-dependent ferroptosis in NSCLC. TMEM164 upregulation synergizes powerfully with anti-PD-1 therapy *in vivo*, demonstrating how engaging this axis can overcome immunotherapy resistance (13). Complementary strategies, such as vaccination with autophagosome-enriched dendritic cells, have also shown efficacy in reducing metastatic burden (81), further supporting the immunostimulatory potential of modulating this crosstalk.

In summary, the autophagy-ferroptosis axis exhibits dual roles in LC biology. It can be hijacked to promote tumorigenesis via stress adaptation, metabolic reprogramming and immune evasion. Conversely, it can be therapeutically engaged to suppress tumors by inducing ferroptotic death and stimulating antitumor immunity.

Persisting unresolved paradoxes underscore the need for a more nuanced understanding. First, the same process can either enhance or subvert antitumor immunity depending on the cellular and cytokine context. Second, some molecular regulators exhibit seemingly contradictory pro-tumor functions despite their ability to induce a tumor-suppressive form of death such as ferroptosis. Therefore, key questions for future research include: i) What are the subtype-specific regulatory networks that dictate the pro- vs. antitumor switch? ii) What are the definitive molecular determinants and microenvironmental cues that establish this context-dependence? iii) What is the mechanistic basis of paradoxical regulators such as HPCAL1? Prioritizing these questions is essential to move beyond descriptive phenomenology and towards the rational design of therapeutic strategies that can reliably steer this dynamic crosstalk toward tumor eradication.

5. Therapeutic strategies targeting the autophagy-ferroptosis axis in LC

Repurposing traditional drugs. Traditional pharmacological agents have demonstrated renewed potential in LC by modulating the autophagy-ferroptosis axis through diverse and sometimes unexpected mechanisms.

Autophagy inhibitors: Chloroquine (CQ) and hydroxychloroquine (HCQ). Antimalarial agents CQ and HCQ are

repurposed for LC by blocking autophagosome-lysosome fusion, thereby blocking autophagic flux (82). Their therapeutic efficacy in LC is markedly subtype-dependent, a critical factor for clinical translation. In NSCLC, HCQ shows promise as both a chemosensitizer and immunomodulator, potentially by reducing lysosomal drug sequestration and boosting $CD8^+$ T-cell responses (83).

Conversely, in a previous study on extensive-stage SCLC, the addition of HCQ to platinum-based chemotherapy failed to improve overall survival and even increased toxicity (84), underscoring that HCQ is not a universal agent and thus necessitates careful patient stratification. Nanodelivery strategies, such as encapsulation in human ferritin nanocages, can potentiate the antitumor activity of HCQ, particularly in cancer with elevated transferrin receptor 1 expression (85). Furthermore, in LKB1/KRAS co-mutant NSCLC, combining HCQ with the MEK inhibitor trametinib synergizes to induce ferroptosis. Paradoxically, autophagy induction under different conditions can confer trametinib resistance by suppressing ferroptosis (86). This bidirectional effect highlights the necessity for context-specific modulation of the autophagy-ferroptosis axis.

Ferroptosis inducers and pathway modulators. Classic ferroptosis inducers such as erastin can surmount radioresistance in NSCLC by triggering ferroptosis (87). The WEE1 G_2 checkpoint kinase inhibitor AZD1775 also blocks cystine uptake and synergizes with SLC7A11 inhibitors to amplify ferroptotic cell death (88). These findings validate the therapeutic targeting of the system Xc^- pathway, although challenges related to tumor selectivity and potential systemic toxicity remain.

Other agents function at the intersection of multiple cell death pathways. The quinoline derivative DFIQ blocks autophagic flux, leading to mitochondrial dysfunction and thereby rendering cells more susceptible to ferroptosis (89). Rabeprazole produces analogous effects and concurrently upregulates markers of pyroptosis, hinting at an uncharacterized tripartite crosstalk among autophagy, ferroptosis and pyroptosis (90). In NSCLC, carbon monoxide (CO) directly triggers ferroptosis through the ROS/GSK3β/GPX4 axis, resulting in the accumulation of LOOH (91). These findings establish the ROS/GSK3β/GPX4 axis as a key driver of CO-induced ferroptosis, but how this pathway intersects with other cell-death pathways remains to be clarified.

Metabolic interventions. Reprogramming cellular metabolism presents another option to adjust ferroptosis sensitivity. Metformin, known primarily for stimulating autophagy and apoptosis via the EGFR/AKT/AMPK/mTOR pathway in SCLC (92), may indirectly influence ferroptosis given the central role of the AMPK/mTOR hub in this crosstalk, although direct evidence is required.

Targeting lipid metabolism is a promising strategy for reversing therapy resistance. The co-administration of ferroptosis inducers and diacylglycerol acyltransferase inhibitors suppresses tumor growth in LC models resistant to multiple chemotherapeutic agents (93). Similarly, modulating homocysteine metabolism through hydrogen sulfide increases ferroptosis susceptibility in NSCLC, although the precise mechanistic link requires further definition (94). These findings collectively validate 'metabolic remodeling' as a viable approach to overcome resistance. A key future direction involves defining optimal drug ratios and identifying predictive biomarkers to guide patient selection for such metabolically targeted combination therapies.

Novel pharmacological agents. Beyond repurposing traditional drugs, the development of novel agents specifically designed to target the autophagy-ferroptosis axis represents a novel option in LC therapy. These efforts focus on distinct regulatory nodes within this interactive network.

Targeting autophagy-related pathways. Research into natural compounds has identified modulators of autophagic signaling as potential antitumor agents in LC. These agents converge on key regulatory nodes: The AMPK/mTOR axis and the Sestrin-2/LKB1/AMPK cascade to provoke autophagy and cell death (95-97). Others, such as corynoxine, target upstream phosphatases such as protein phosphatase 2A to dually inhibit AKT signaling (98), whereas Gboxin and its analog Y9 trigger lysosomal dysfunction and autophagic impairment (99). However, a critical gap across these studies is the general lack of investigation into whether and how these autophagy-modulating agents affect ferroptosis, which limits the assessment of their full relevance to the core crosstalk theme. Furthermore, the tumor selectivity and potential off-target toxicity of agents such as Gboxin on normal lung epithelium remain unclear, posing challenges for clinical translation.

Targeting ferroptosis and shared regulatory nodes. Drug development has also progressed towards core components of the ferroptosis pathway and its key intersections with autophagy. Targeting the upstream autophagy initiator ULK1/2 presents a strategic node. The selective ULK1/2 inhibitor, DCC-3116, synergizes with the $KRAS^{G12C}$ inhibitor sotorasib to suppress KRAS-driven LC, whereas this combination has been assessed only in early preclinical stages and lacks predictive biomarkers for patient stratification (17). By contrast, hesperetin inhibits ferritinophagy and mitigates ferroptosis by modulating the PI3K/AKT/mTOR/ULK1 pathway (100), further underscoring the context-dependent role of ULK1.

Inhibition of the antioxidant transcription factor NRF2 is another validated strategy to enhance ferroptosis sensitivity. The NRF2 inhibitor, ML385, synergizes with silymarin (101), and NRF2 knockdown facilitates S-3'-hydroxy-7',2',4'-trimethoxyisoflavone-mediated ferritinophagy (102), revealing a reciprocal regulatory loop between NRF2 and autophagy. Other agents include sanggenol L, which acts through the miR-26a-1-3p/MDM2/p53/SLC7A11 axis (103), and curcumin, which activates autophagy to subsequently trigger ferroptosis (75). Polyoxometalates exhibit synergistic anti-NSCLC activity with ferroptosis and apoptosis inducers (104), although the specific nodes of crosstalk involved remain to be defined.

Optimizing ferroptosis inducers. To address the pharmacokinetic and selectivity limitations of classic ferroptosis inducers, advanced formulation strategies are being explored. A folic acid-modified liposomal nanoformulation co-delivering erastin and the metallothionein 1D pseudogene markedly augments bioavailability and cytotoxicity in LC (105). Concurrently, understanding resistance mechanisms is crucial. Upregulation of the SLC7A11/HOXB9 axis can mitigate cold atmospheric plasma-induced ferroptosis while

fueling tumor progression (106). Conversely, inducing ferroptosis sensitizes LC cells to IFN-γ secreted by ROR1-targeted chimeric antigen receptor (CAR)-T cells, revealing a potent synergy with immunotherapy (107). A recurring limitation in both therapeutic development and resistance studies is the failure to consider the potential contributory role of autophagy, leaving the integrated network perspective incomplete.

Gene therapy

Gene editing technologies. The advent of precision gene-editing tools, notably CRISPR-Cas9, has enabled the direct targeting of specific nodes within the autophagy-ferroptosis regulatory network. This approach allows for the functional characterization of key genes and the exploration of their therapeutic potential. For example, CRISPR-Cas9-mediated knockout of the anti-apoptotic gene Bcl-2 triggers ferroptosis in LUAD cells by disrupting the Bax/voltage-dependent anion channel axis (108). Similarly, targeting the central ferroptosis inhibitor SLC7A11, the expression of which is upregulated via the MISP/MST/yes-associated protein signaling pathway, represents a rational strategy to sensitize cells to ferroptosis (109). Beyond ferroptosis-specific genes, editing regulators of autophagy can also influence this crosstalk. Ablation of DEAD-box helicase 24 facilitates autophagy through NF-κB-mediated transcriptional upregulation of Beclin-1 (110). While these studies provide compelling proof-of-concept, a notable translational gap exists. Most findings are derived from *in vitro* models, underscoring the urgent need for robust *in vivo* validation in relevant preclinical models. Furthermore, future research should prioritize exploring synergistic combinations of such genetic interventions with pharmacological modulators of autophagy or ferroptosis to achieve enhanced therapeutic efficacy.

Gene delivery vectors. Effective gene therapy requires advanced delivery vectors. While viral vectors offer high efficiency, their immunogenicity and limited cargo capacity pose notable drawbacks. By contrast, non-viral vectors, including liposomes and polymeric nanoparticles, provide improved biocompatibility and lower immunogenicity, although often at the expense of reduced transfection efficiency (111).

To overcome these limitations, multifunctional nanomaterial-based platforms have emerged as promising alternatives. These systems can simultaneously act as gene carriers and therapeutic agents. For example, Cu_2O@Au nanozymes deplete intracellular GSH and downregulate SLC7A11, thereby provoking ferroptosis (112). Iron-platinum alloy nanoparticles have been shown to reverse tyrosine kinase inhibitor (TKI) resistance by activating ferroptosis (113). Other engineered nanocarriers are designed either to co-activate both ferroptosis and autophagy (114) or to synergistically combine chemotherapeutic agents such as paclitaxel with ferroptosis induction (115).

Despite their promising preclinical performance, the clinical translation of nanocarriers faces notable hurdles. Key challenges include unresolved long-term biosafety profiles, the absence of standardized large-scale manufacturing protocols, and the insufficient investigation into their potential effects on autophagy and ferroptosis in normal tissues. Addressing these issues is therefore paramount to realizing the full potential of nanomaterial-mediated gene therapy in LC.

Combination treatment strategies. Beyond monotherapies, the strategic modulation of autophagy and ferroptosis offers a powerful approach to augment the efficacy of established cancer treatments and overcome resistance to them. The following sections detail how this axis interacts with and can be leveraged to enhance chemotherapy, radiotherapy, targeted therapy and immunotherapy.

With chemotherapy. Chemotherapy efficacy in LC is frequently constrained by drug resistance, which can be alleviated by tuning the autophagy-ferroptosis interplay. The role of autophagy is particularly context-dependent. It can serve as a cytoprotective mechanism, promoting resistance, as seen in SCLC where upregulation of lncRNA LYPLAL1-DT enhances autophagy and contributes to multidrug resistance (116). Furthermore, suppressing such protective autophagy can be beneficial, exemplified in NSCLC where silencing staphylococcal nuclease and tudor domain containing 1 sensitizes cells to various agents by downregulating PDCD4 (117). By contrast, in a mouse model of NSCLC, inactivation of the essential autophagy gene ATG5 has been shown to accelerate the early stages of oncogenesis (118). This divergence underscores the need for subtype-specific targeting of autophagy.

Concurrently, inducing ferroptosis has proven effective in surmounting chemoresistance. Suppression of SPTBN2 or enhancement of HAR1A-mediated MYC degradation increases cisplatin sensitivity by inhibiting adaptive autophagy or directly triggering ferroptosis (119,120). Furthermore, targeting regulators within the crosstalk itself, such as knocking down deltex E3 ubiquitin ligase 2 to stabilize NCOA4 and promote ferritinophagy, can mitigate cisplatin resistance in NSCLC (121). Fig. 2 depicts the mechanisms underlying the regulation of autophagy and ferroptosis crosstalk in the context of LC and LC pharmacotherapy. These findings collectively validate that precise intervention in this axis may markedly augment chemotherapeutic efficacy, though the successful clinical translation of such combinations require careful patient stratification based on molecular and histological subtypes.

With radiotherapy. Modulating the autophagy-ferroptosis axis also represents a viable strategy to counteract radioresistance, as it functions bidirectionally to either sensitize cells or promote resistance.

Several mechanisms have been identified to augment radiosensitivity through ferroptosis induction. For example, miR-139 increases the radiosensitivity of NSCLC by directly targeting cJUN and KPNA2, disrupting the NRF2 pathway and amplifying radiation-induced lipid peroxidation (122). Similarly, targeting NRF2 to upregulate phosphorylase kinase catalytic subunit γ2 promotes ferritinophagy and mitochondrial stress-dependent ferroptosis, increasing radiosensitivity (123). MAF bZIP transcription factor F enhances sensitivity to both cisplatin and ionizing radiation by regulating SLC7A11, CDK6 and CDKN2C to induce ferroptosis and arrest the cell cycle (124).

Conversely, certain pathways activated by radiotherapy can promote resistance via pro-survival autophagy. Upregulation of long-chain acyl-CoA synthase (ACSL)6 enhances post-radiotherapy invasiveness in LC by augmenting FLI1-collagen-mediated autophagic flux (125). Lactoferrin establishes a positive feedback loop involving

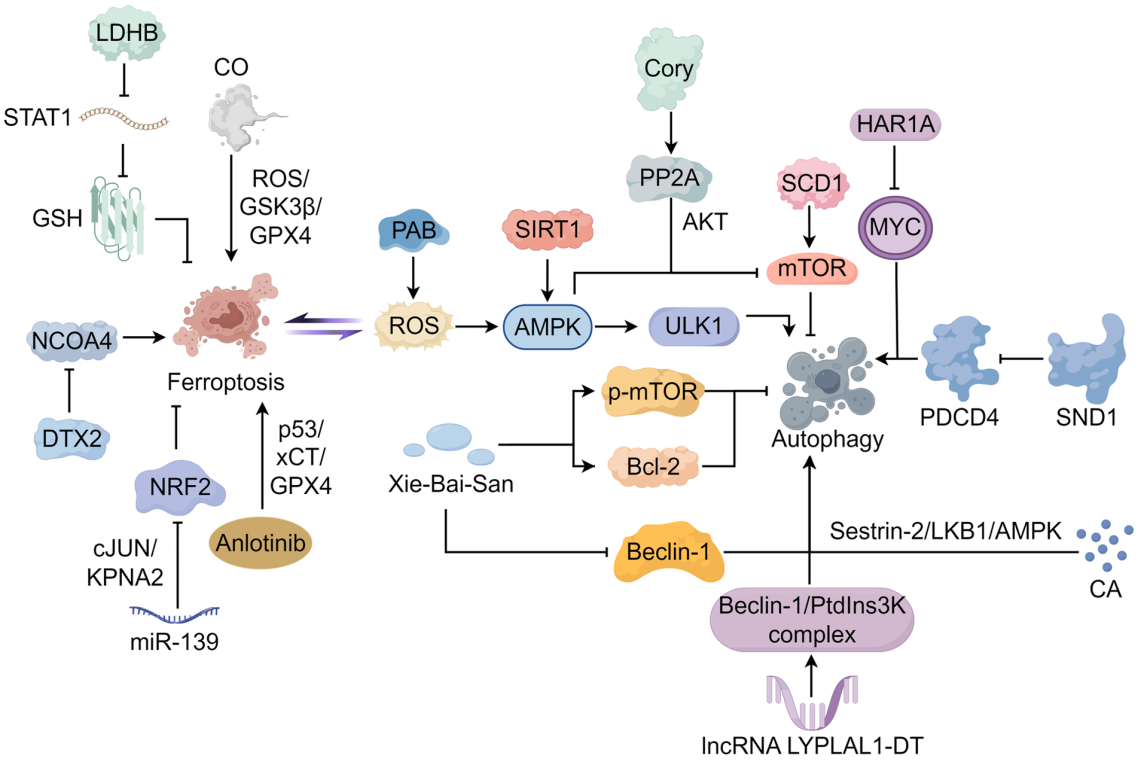

Figure 2. Mechanisms of the crosstalk regulation between autophagy and ferroptosis in lung cancer and lung cancer pharmacotherapy. The figure was created by Figdraw (www.figdraw.com). LDHB, lactate dehydrogenase B; GSH, glutathione; CO, carbon monoxide; PAB, pseudolaric acid B; ROS, reactive oxygen species; Cory, corynoxine; PP2A, protein phosphatase 2A; ULK1, unc-51 like kinase 1; SCD1, stearoyl-CoA desaturase 1; SND1, staphylococcal nuclease and tudor domain containing 1; PDCD4, programmed cell death 4; CA, carnosic acid; lncRNA, long non-coding RNA; p-mTOR, phosphorylated mechanistic target of rapamycin; miR-139, microRNA-139; NRF2, nuclear factor, erythroid 2 like 2; DTX2, deltex E3 ubiquitin ligase 2; NCOA4, nuclear receptor coactivator 4.

AMPK/SP2/NEAT1/miR-214-5p to foster autophagy and contribute to radioresistance in lung squamous cell carcinoma (126). These opposing effects highlight how the net impact of the crosstalk on radiosensitivity is determined by specific molecular contexts, presenting both a challenge and an opportunity for personalized radiosensitization strategies.

With targeted therapy. Targeted therapy resistance, a major clinical challenge, is amenable to intervention via the autophagy-ferroptosis axis, a key determinant of cell fate under stress, through two primary strategies. i) Inducing ferroptosis to reverse targeted therapy resistance.

Ferroptosis induction has demonstrated considerable potential to circumvent resistance to targeted therapies, particularly in EGFR-mutant and KRAS-driven LC.

In EGFR-mutant NSCLC, multiple approaches have been shown to restore sensitivity by activating ferroptosis. For example, Tenovin-3 triggers mitochondrial pathway-dependent ferroptosis in EGFR 19del cells (127). Downregulation of apoptosis-associated tyrosine kinase promotes iron accumulation via enhanced endosome recycling, sensitizing EGFR-TKI-resistant cells to ferroptosis inducers such as RSL3 (128). Beyond classic TKIs, the multi-targeted agent anlotinib exerts potent antitumor effects in NSCLC by specifically inducing ferroptosis via the p53/xCT/GPX4 axis (129). Conversely, upregulation of the anti-apoptotic protein MCL1 has been linked to acquired resistance against sorafenib-induced ferroptosis, revealing a potential adaptive mechanism (130).

In KRAS-driven LC, targeting metabolic dependencies provides another strategic entry point. Inhibition of LDHB upregulates STAT1, suppresses SLC7A11 expression and disrupts GSH metabolism, thereby surmounting intrinsic ferroptosis resistance in this subtype (131).

Collectively, these studies establish ferroptosis induction as a viable strategy to overcome targeted therapy resistance. They reveal actionable targets spanning signaling, metabolic, and vesicular recycling pathways, offering a robust foundation for designing novel drug combinations.

ii) Modulating autophagy to overcome drug resistance. Targeting autophagy represents another critical strategy to overcome resistance to targeted therapies. Its role is context-dependent, functioning as either a pro-survival mechanism that confers resistance or a process that can be co-opted to enhance drug sensitivity. Autophagy can be co-opted by cancer cells to drive resistance to EGFR-TKIs. For example, PD-L1 upregulation activates pro-survival autophagy via the MAPK pathway, contributing to gefitinib resistance and NSCLC progression (132). Similarly, autophagy mediated by the STAT3/FOXM1/ATG7 axis has been identified as a novel mechanism underlying icotinib resistance (133). Pharmacological inhibition of such pro-survival autophagy can restore drug sensitivity. The traditional formulation Xie-Bai-San, for example, suppresses gefitinib-induced autophagic flux by modulating the mTOR/Beclin-1 pathway, thereby blocking this escape route (134). Beyond direct suppression, strategic combination therapies can redirect cellular responses. The concurrent inhibition of MEK (trametinib) and glutamine

metabolism (V-9302) enhances antitumor efficacy by orchestrating the FOXO3a/FOXM1 axis and autophagy, leading to pyroptosis and cell cycle arrest (135).

A similar duality is observed in ALK-rearranged NSCLC. While ALK inhibition itself can trigger an LC3B-independent macroautophagic flux that promotes the survival of EML4-ALK$^+$ cells (136), strategically inducing autophagy in a controlled manner can be beneficial. Activating SIRT1 upregulates AMPK, inhibits mTOR phosphorylation and induces autophagy, thereby sensitizing EML4-ALK mutant cells (L1196M, G1202R) to crizotinib (137).

These findings underscore the complex, dual role of autophagy in targeted therapy resistance. The central challenge lies in precisely determining whether to inhibit or activate autophagic pathways, a decision that depends on the specific molecular context, including the driver mutation and the resistance mechanism at play.

Combination with immunotherapy. Patient selection for combination strategies is critical. In NSCLC, 18F-RGD uptake detected by PET is negatively associated with tumoral PD-L1 expression (138), a finding that may inform patient selection for combined immunotherapy and autophagy-ferroptosis modulation. The integration of immune checkpoint inhibitors (ICIs) with modulators of autophagy and ferroptosis has emerged as a promising strategy to overcome resistance to immunotherapy in LC. This approach seeks to enhance tumor immunogenicity, reactivate antitumor immunity and improve durable clinical responses. i) Modulating autophagy to improve immunotherapeutic efficacy. Autophagy exerts a dual influence on tumor-immune interactions, which can be strategically modulated to overcome ICI resistance. On one hand, induction of autophagy can promote the degradation of immunosuppressive proteins. For example, the PPARγ-LC3 interaction facilitates autophagic degradation of PD-L1 in lysosomes, thereby attenuating immune evasion in NSCLC (139). Similarly, the small molecule USP24-i-101 facilitates autophagy-dependent PD-L1 degradation and may help mitigate acquired resistance to ICIs (140). On the other hand, tumor cells can exploit autophagy as a protective mechanism. Under glutamine-depleted conditions in the tumor microenvironment, autophagy mediates degradation of the IFN-γ receptor, impairing IFN-γ signaling and contributing to resistance against anti-PD-1/PD-L1 therapy (141). This duality underscores the importance of context-specific modulation and highlights the current lack of reliable biomarkers to guide patient selection for autophagy-targeting combinations.

ii) Inducing ferroptosis to synergize with immunotherapy. Ferroptosis inducers can potentiate immunotherapy by triggering immunogenic cell death, releasing tumor antigen and activating antitumor immune responses. For example, combining ROR1-targeted CAR-T cells with ferroptosis inducers enhances lipid peroxidation and augments antitumor efficacy in a mouse model of NSCLC (107). The natural compound fascaplysin induces both apoptosis and ferroptosis, thereby sensitizing NSCLC to anti-PD-1 therapy (142). Moreover, the protein LRRC1B has been shown to modulate ICI efficacy by regulating ferroptosis sensitivity in NSCLC cells (143). However, excessive or systemic induction of ferroptosis may cause normal tissue toxicity and impair immune cell function, emphasizing the need for precise spatiotemporal control in therapeutic regimens.

The toxicities of ferroptosis inducers manifest as systemic iron overload and lipid peroxidation-mediated multi-organ injury, requiring rigorous longitudinal monitoring and dynamic management (11). Beyond classic bone-marrow suppression and transaminase elevation, four pulmonary-specific and systemic hazards demand particular vigilance in patients with LC: Radiation-like pneumonitis/fibrosis, iron-catalyzed oxidative stress, CD8$^+$ T-cell functional exhaustion and QT-interval prolongation (144).

iii) Coordinated targeting of autophagy and ferroptosis. Simultaneous modulation of autophagy and ferroptosis may yield synergistic benefits and overcome compensatory resistance mechanisms. For example, combining radiotherapy with PD-L1 blockade and autophagy inhibition activates the cGAS-STING pathway and promotes T-cell-mediated antitumor immunity (145). Activation of the cGAS-STING pathway in tumor cells can further induce ferroptosis (146). Conversely, in cancer stem cells, the CPT1A/c-Myc feedback loop activates the NRF2/GPX4 axis and downregulates ACSL4, thereby suppressing ferroptosis and potentially diminishing immunotherapeutic response (147). Notably, NRF2 promotes autophagosome formation and enhances autophagic activity, which in turn inhibits apoptosis in NSCLC cells (148). These findings illustrate the therapeutic potential of dual-pathway intervention, although the complex interplay between autophagy, ferroptosis and various immune cell populations requires further mechanistic elucidation to optimize combination strategies. Fig. 3 depicts the involvement of autophagy and ferroptosis across major therapeutic modalities in LC. As illustrated in Table I, most therapeutic strategies remain in the preclinical stage.

Targeting the autophagy-ferroptosis axis represents a rational and evolving approach to potentiate the efficacy of immunotherapy in LC. Successful clinical translation will depend on identifying predictive biomarkers, optimizing the timing and sequence of combination therapies, and developing agents capable of selectively modulating these pathways within the tumor microenvironment.

6. Research challenges and future perspectives

Current challenges. Notable challenges persist in translating the autophagy-ferroptosis axis into clinical applications for LC, despite growing mechanistic understanding. The primary hurdle is the intrinsic complexity and context-dependency of this interplay. Its regulatory network remains incompletely mapped, as it involves numerous overlapping and often contradictory signaling pathways. A critical gap is the identification of definitive molecular switches that determine whether the crosstalk promotes tumor cell survival or death in a given therapeutic setting, which severely impedes the rational design of pathway-specific modulators.

Substantial inter- and intra-tumoral heterogeneity, epitomized by the profound biological divergence between LUAD and SCLC (149), remains a major obstacle to developing universal treatment paradigms. Although multimodal regimens combining radiotherapy, chemotherapy and immunotherapy have achieved notable clinical benefits across LC subtypes (150), the molecular drivers of these differential responses remain

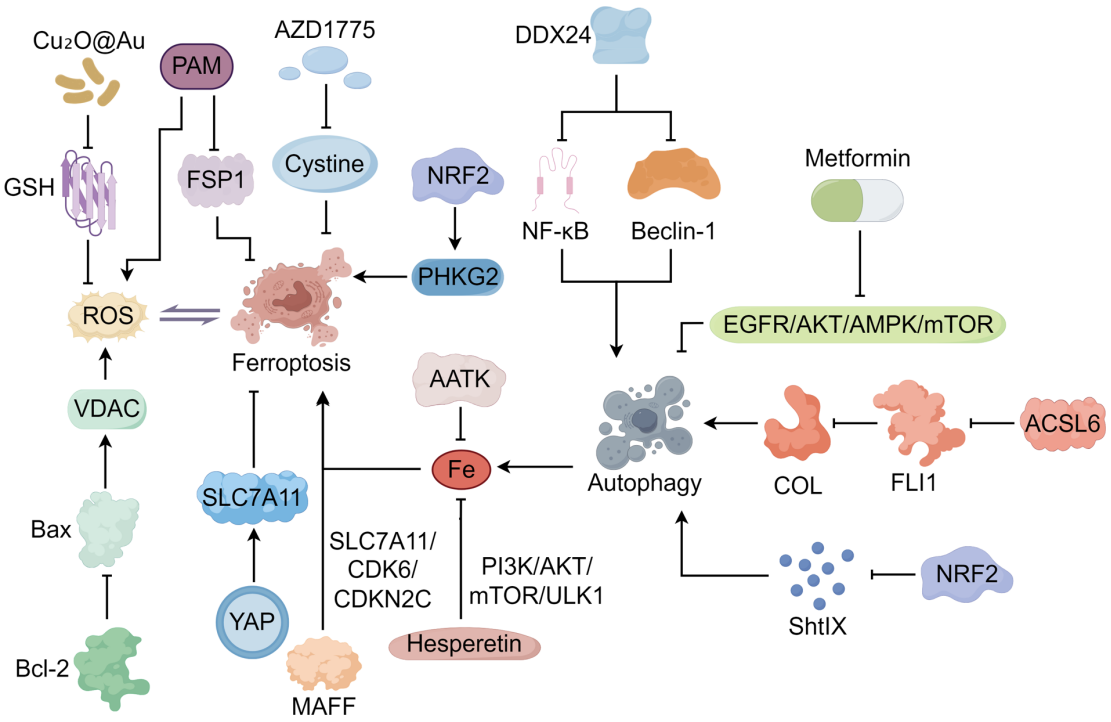

Figure 3. Mechanisms of autophagy and ferroptosis in lung cancer gene therapy, targeted therapy and immunotherapy. The figure was created by Figdraw (www.figdraw.com). GSH, glutathione; ROS, reactive oxygen species; PAM, plasma-activated medium; FSP1, ferroptosis suppressor protein 1; NRF2, nuclear factor, erythroid 2 like 2; PHKG2, phosphorylase kinase catalytic subunit γ2; DDX24, DEAD-box helicase 24; ACSL6, long-chain acyl-CoA synthase 6; COL, collagen; AATK, apoptosis-associated tyrosine kinase; ShtIX, S-3-hydroxy-7',2',4'-trimethoxyisoflavone; MAFF, MAF bZIP transcription factor F; YAP, Yes-associated protein; SLC7A11, solute carrier family 7 member 11; VDAC, voltage-dependent anion channel.

poorly understood. This knowledge gap represents a critical barrier to advancing truly precision-based therapeutic strategies.

Most therapeutic interventions remain in preclinical development, with clinical translation hindered by two key barriers: The lack of validated biomarkers for patient stratification and incomplete elucidation of synergistic combination mechanisms. A central, unresolved question remains how to precisely balance the modulation of autophagy and ferroptosis to maximize therapeutic efficacy while minimizing the risks of tumor promotion or off-target tissue damage.

Future directions and prospects. To tackle these barriers, future research should prioritize the following key areas.

Deciphering context-specific regulatory networks. Employing integrated multi-omics approaches across diverse LC subtypes and dynamic treatment states is essential. This will enable the construction of a high-resolution map of the molecular landscape, the identification of subtype-specific regulatory nodes and switches (151), and address the fundamental knowledge gaps highlighted in preceding sections, thereby laying a foundation for precise therapeutic targeting.

Development of predictive biomarkers. Predictive biomarkers, particularly those linked to key regulatory axes such as NRF2/p62, COX7A1 or USP13, require urgent discovery and clinical validation to reliably predict sensitivity to ferroptosis inducers or autophagy modulators. Correlating longitudinal multi-omics data from large, well-annotated patient cohorts with clinical outcomes will thus enable accurate patient stratification, guide therapeutic decision-making, and increase the success rate of clinical trials.

Leveraging artificial intelligence (AI) and integrative analytics. Advanced computational approaches, including AI and machine learning algorithms, are increasingly employed to decipher the heterogeneity of autophagy-ferroptosis regulation and optimize therapeutic decisions by integrating multimodal data (genomics, transcriptomics, proteomics and clinical data) (152,153). Their core value is concentrated in three key directions, as follows: i) Deep learning, network-based machine learning and other algorithms are utilized to mine patient-specific autophagy-ferroptosis molecular signatures, enabling precise stratification of treatment responders and non-responders, and providing a basis for individualized therapeutic target selection (153). ii) AI models trained on longitudinal clinical and molecular data integrate molecular features and clinical variables to predict individual sensitivity to specific therapeutic regimens, reducing reliance on therapeutic trial and error, and optimizing drug dosage and sequence (154). iii) AI-driven real-time analytical technologies monitor dynamic reprogramming in crosstalk pathways during treatment, guiding timely adjustments to therapeutic strategies and effectively overcoming inter-patient variability in treatment responses among advanced patients (155,156).

These technologies may accelerate the discovery of novel therapeutic targets and the development of personalized regimens, serving as critical cutting-edge tools to advance autophagy-ferroptosis-targeted therapy from basic research to clinical translation.

Advancing translational and clinical research. Building upon the mechanistic foundations, translational efforts must now focus on: i) Optimizing the pharmacokinetics, biodistribution and safety profiles of advanced delivery systems;

Table I. Representative compounds targeting autophagy-ferroptosis crosstalk in lung cancer: Mechanisms and research stages.

First author, year	Compound/agent	Targeted mechanism	Research stage	(Refs.)
Mauthe, 2018	Chloroquine	Inhibits autophagosome-lysosome fusion, blocks autophagic flux	*In vitro* and *in vivo*	(82)
Li, 2018	HCQ	Reduces lysosomal drug sequestration and enhances $CD8^+$ T-cell responses	Random phase II multicenter trial	(83)
Fang, 2024	HFn@HCQ (nanocarrier)	Targeted delivery of HCQ, enhances autophagy inhibition	*In vitro* and *in vivo*	(85)
Pan, 2019	Erastin	Inhibits system Xc^-, depletes GSH, induces GPX4-mediated ferroptosis; overcomes radioresistance in NSCLC	*In vitro*	(87)
Tang, 2021	Curcumin	Induces iron overload, GSH depletion and lipid peroxidation	*In vitro*	(75)
Liu, 2025	Rabeprazole	Inhibits autophagy, triggers pyroptosis and ferroptosis	*In vitro* and *in vivo*	(90)
Xu, 2024	ML385	Inhibits NRF2, enhances ferroptosis sensitivity	*In vitro*	(101)
Fu, 2024	Sanggenol L	Regulates miR-26a-1-3p/MDM2/p53/SLC7A11 axis, induces ferroptosis	*In vitro* and *in vivo*	(103)
Xia, 2025	Metformin	Induces autophagy via EGFR/AKT/AMPK/mTOR pathway in SCLC	*In vitro* and *in vivo*	(92)
Zheng, 2024	Hydrogen sulfide	Regulates homocysteine metabolism, enhances ferroptosis in NSCLC	*In vitro* and *in vivo*	(94)
Gai, 2020	Folate-modified liposome (erastin + MT1DP)	Enhances ferroptosis sensitivity via miR-365a-3p/NRF2 axis	*In vitro* and *in vivo*	(105)
Tsai, 2024	Iron-platinum alloy nanoparticles	Reverses TKI resistance by activating ferroptosis	*In vitro* and *in vivo*	(113)
Luo, 2024	Pseudolaric acid B	Modulates ROS/AMPK/mTOR/autophagy pathway	*In vitro* and *in vivo*	(95)
Hou, 2024	Corynoxine	Activates PP2A, inhibits AKT-mTOR/GSK3β axes, induces autophagic cell death	*In vitro* and *in vivo*	(98)
Bhatt, 2023	HCQ + trametinib	Inhibits autophagy and blocks the MEK pathway, synergistically induces ferroptosis in LKB1/KRAS co-mutant NSCLC	*In vitro* and *in vivo*	(86)
Li, 2025	ROR1-targeted CAR-T cell therapy + ferroptosis inducers	Enhances lipid peroxidation and antitumor efficacy	*In vitro* and *in vivo*	(107)
Ma, 2024	Xie-Bai-San	Inhibits autophagy (via the mTOR/Beclin-1 pathway), reverses gefitinib resistance	*In vitro* and *in vivo*	(134)
Liu, 2025	Trametinib + V-9302	Regulates the FOXO3a/FOXM1 axis and autophagy, induces pyroptosis/cell cycle arrest	*In vitro* and *in vivo*	(135)
Liu, 2024	DTX2 knockdown	Stabilizes NCOA4, promotes ferritinophagy and reverses cisplatin resistance in NSCLC	*In vitro* and *in vivo*	(121)
ALMatrafi, 2025	TMEM164 overexpression	Activates autophagy-dependent ferroptosis and synergizes with anti-PD-1 to enhance antitumor immunity	*In vitro* and *in vivo*	(13)
Yang, 2024	Crizotinib + SIRT1 activation	Upregulates AMPK, inhibits mTOR and induces autophagy to sensitize EML4-ALK mutant cells	*In vitro*	(137)

HCQ, hydroxychloroquine; GSH, glutathione; NSCLC, non-small cell lung cancer; MT1DP, metallothionein 1D pseudogene; GPX4, glutathione peroxidase 4; NRF2, nuclear factor, erythroid 2 like 2; SCLC, small cell lung cancer; miR, microRNA; SLC7A11, solute carrier family 7 member 11; mTOR, mechanistic target of rapamycin; TKI, tyrosine kinase inhibitor; ROS, reactive oxygen species; PP2A, protein phosphatase 2A; DTX2, deltex E3 ubiquitin ligase 2; NCOA4, nuclear receptor coactivator 4; CAR-T, chimeric antigen receptor-T; TMEM164, transmembrane protein 164.

ii) conducting large-scale, biomarker-driven clinical trials to evaluate rational combination therapies; and iii) exploring the underexplored role of the autophagy-ferroptosis crosstalk in critical clinical processes such as metastasis, tumor dormancy and therapy-resistant recurrence.

7. Conclusion

The dynamic crosstalk between autophagy and ferroptosis represents a promising frontier for innovating LC therapeutic strategies. While notable scientific and translational challenges remain, concerted efforts to elucidate context-dependent mechanisms, develop precision biomarkers and tools, and rigorously evaluate targeted combinations in the clinic are poised to yield transformative advances. Success in this endeavor may result in the identification of effective, durable and safer therapeutic paradigms, ultimately improving outcomes and quality of life for patients with LC.

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Authors' contributions

RS designed the research and analyzed the literature. YZ drafted the manuscript. Data authentication is not applicable. Both authors contributed to literature collection, drafting and revising the manuscript, and have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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